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## Nutritional Anaemia

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### 1. Introduction

Data available in Australia regarding the prevalence of iron deficiency anaemia (IDA) in pregnant women show that about 17.4% of pregnant women suffer from IDA, while the World Health Organization (WHO) global database on anaemia has suggested a prevalence of 14% based on a regression-based analysis.

There is a suggested association between IDA and the following maternal risks: increased fatigue antenatally and postnatally, poor exercise tolerance, impaired thermoregulation, decreased resistance to infection, reduced tolerance of bleeding or surgical intervention at delivery, delayed instigation of lactation and increased risk of postnatal depression. IDA is also a risk factor for preterm delivery and subsequent low birth weight and may be associated with inferior neonatal health. Infants born to women with IDA are more likely to become anaemic themselves which, in turn, is known to have a detrimental effect on an infant's mental and motor development. Although iron supplementation during pregnancy is one of the most widely practiced public health measures, there remain many controversial issues with this practice.

Oral iron supplementation has long been a standard treatment for IDA worldwide. However, patients do not always respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, which can play a significant role in rates of compliance. The side effects include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhoea, and or constipation, and occur in large cohort of patients taking iron preparations. In addition, the presence of bowel disease can affect the absorption of iron and thereby minimize the benefit received from oral iron therapy.

In the past, intravenous iron had been associated with undesirable and sometimes serious side-effects and was therefore limited in use. In recent years, the new type II and III iron complexes have been developed which are better tolerated and can be used for a rapid reversal of iron deficiency anaemia. Despite increasing evidence of the safety of the newer preparations, intravenous iron continues to be underutilized.

#### 1.1 Iron deficiency anaemia in the general population

Anaemia occurs in different age groups in a number of clinical situations associated with iron deficiency, iron deficiency anaemia and blood loss. Usually in the presence of intact

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erythropoiesis iron therapy is very effective in restoring the depleted iron stores and accordingly improving the haemoglobin. Other treatment strategies that stimulate erythropoiesis such as erythropoietin will also require the presence of iron in order to be an effective treatment. Intravenous iron offers a rapid repletion of iron and is superior to oral iron as proven in many clinical trials.

In this regard, we will describe different clinical scenarios for iron deficiency anaemia in different cohorts of patients and numerate the available management options in the literature.

### **1.2 Other causes for nutritional anaemia**

In this part, we are discussing other common nutritional deficiencies apart from iron that result in anaemia such as vitamin B12 and folate deficiencies. Furthermore, we discuss rare nutritional anaemia due to copper and selenium deficiencies and highlighting the most appropriate management approaches and treatment strategies.

## **2. Iron deficiency**

Nutritional iron deficiency is the most common deficiency disorder in the world, affecting more than two billion people worldwide, with pregnant women at particular risk.<sup>1-3</sup> World Health Organization (WHO) data show that iron deficiency anaemia (IDA) in pregnancy is a significant problem throughout the world with a prevalence ranging from about 15% of pregnant women in industrialized countries to an average of 56% in developing countries (range 35-75%).<sup>2,3</sup>

Furthermore, IDA is affecting a large number of children and women not only in the developing world, but is also considered the only nutrient deficiency that is significantly prevalent in the developed world too. The numbers of patients with ID and IDA are overwhelming as more than 2 billion people, over 30% of the world's population, are iron deficient with variable prevalence, distribution and contributing factors in different parts of the world.<sup>1-3</sup>

Iron deficiency affects more people than any other condition, constituting an epidemic public health crisis. It is usually present with subtle manifestations and sometimes considered as a chronic slowly progressing disease that is often underestimated and untreated worldwide despite several warnings and awareness efforts of the World Health Organisation.<sup>1-3</sup>

It is worth noting that IDA has a debilitating effect as it reduces the work capacity of individuals and perhaps entire populations, with resultant serious economic consequences and obstacles to national development.<sup>1,4-6</sup>

The high prevalence of IDA has substantial health consequences with subsequent socio-economic hazards, including poor pregnancy outcome, impaired educational performance, and decreased work capacity and productivity.<sup>1,6</sup>

Targeted iron supplementation, iron rich diet, or both, can improve iron deficiency. However, variability of bioavailable iron compounds limit its value against nutritional iron deficiency. Therefore, laboratory measures of iron stores should be utilised to determine iron deficiency and monitor the therapy.<sup>3,4,6</sup>

Iron deficiency anaemia is quite often underestimated despite the high prevalence of iron deficiency. Blood loss is a major cause of anaemia in the general population.<sup>5,6</sup> This review

highlights the importance of early diagnosis of IDA and hence offers the most appropriate treatment in order to avoid serious complications of anaemia.

### 2.1 Causes of iron deficiency anaemia

Nutritional iron deficiency generally arises when physiological requirements cannot be met by daily dietary iron ingestion as well as iron absorption. Religious beliefs in some countries and the dietary attitude of individuals may contribute to lack of iron supply when certain populations consume monotonous plant-based diets and hence reduces dietary iron bioavailability.

Women are at particular risk for developing IDA especially in their childbearing period as they have greater iron requirement because of menstrual blood loss and also during the pregnancy and lactation period when they have increased iron demands.<sup>2</sup>

Iron deficiency can also be caused by other types of chronic blood loss including gastrointestinal blood loss from gastritis, peptic ulcers, inflammatory bowel disease, parasitic infestations (such as *hookworms*, *Ancylostoma*) as well as haemorrhoids.<sup>7</sup>

The recommended dietary daily iron for men over the age of puberty and women over the age of menopause are 8 mg per day, while for women in the child bearing period the recommended daily dietary iron dose is 18 mg per day.<sup>8</sup> In the typical diet, major sources of iron are meat, poultry, nuts and seeds, legumes and bean products, green leafy vegetables, raisins, whole grains and fortified cereals.<sup>8</sup>

### 2.2 Symptoms of iron deficiency

The presenting symptoms of IDA are variable and usually are the general symptoms of anaemia, including lethargy; unusual fatigue after exertion; signs of iron deficiency including paleness of the skin or eyes, intestinal problems, cognitive problems such as impaired learning ability, spoon nails, easy brittle and fragile nails, leg cramps especially in night time (restless leg syndrome) and sometimes hair loss.<sup>6,7</sup>

### 2.3 Diagnosis of Iron deficiency

Although a study of bone marrow iron stores is an accurate tool for assessing the body stored iron, it remains an impractical, invasive procedure to apply for most patients.

Measurement of both soluble transferrin receptor and serum ferritin provide a tool for accurate diagnosis of IDA. However, transferrin receptor is not a well-standardized test that can be reliably reproduced with high precision in most of laboratories worldwide.

In the meantime, ferritin estimation is an easy automated test to perform in most laboratories in the world; however its use is limited in case of inflammation or infection as it is considered as an acute phase reactant that is affected by many conditions including inflammation or infection and hence negatively influences its value.

Therefore, new technology such as hypochromic reticulocytes and reticulocyte haemoglobin testing, reportedly have higher sensitivity, specificity, reproducibility and cost effectiveness as a screening tool for iron deficiency.<sup>9,10</sup> This may offer a reliable screening test for iron deficiency in the future.

### 2.4 Iron metabolism

The main source of iron in humans comes from the destruction of erythrocytes by macrophages of the reticuloendothelial system including the spleen (recycled internal iron

supply), while the daily requirement of external iron remains as little as between 1 to 8 mg daily. However, more external iron is required in case of increased demand for iron such as physiological requirements during growth, pregnancy or in a pathological condition such as bleeding (increase iron loss).<sup>3,4,6,8</sup> Recent studies have shown how the human body up- and down-regulate iron absorption in response to changing iron status via intestinal and hepatic proteins.<sup>6,10</sup>

Transferrin is an important protein synthesized by the liver that provides both a high affinity and high avidity mechanism to increase iron yield required for active erythropoiesis.<sup>11</sup>

Hepcidin is a peptide hormone that is also synthesized by liver that regulates iron and plays a significant role in iron metabolism.<sup>12-15</sup> Hepcidin was first described in January 1998 by Tomas Ganz and colleagues,<sup>12</sup> who sequenced this peptide and found that it contained 25 amino acids and 4 disulfide bonds. This peptide circulates in the plasma and responds to various stimuli that regulate iron stores and serum iron and is usually renally excreted.<sup>13</sup>

Ferroportins are considered as hepcidin receptor/iron exporter in the regulation of iron absorption, recycling, and tissue distribution. Ferroportin 1A (FPN1A) works as an element for translational repression in iron-deficient cells, while FPN1B is expressed in duodenal enterocytes, enabling them to export iron.<sup>12</sup>

Hepcidin, controls ferroportin and hence, the inflows of iron into plasma from main sources; duodenal enterocytes absorbing iron intake and from macrophages involved in the recycling of iron as well as from hepatocytes involved in iron storage.<sup>12-15</sup>

During pregnancy, fetal hepcidin controls the placental transfer of iron from maternal plasma to the fetal circulation. When hepcidin concentrations are low, iron enters blood plasma at a high rate. When hepcidin concentrations are high, ferroportin is internalized, and iron is trapped in enterocytes, macrophages, and hepatocytes.<sup>14,15</sup>

Plasma iron concentrations and transferrin saturation are usually reflecting the difference between the hepcidin and ferroportin-regulated transfer of iron to plasma and iron consumption by the erythropoietic bone marrow tissue and, to a lesser extent, other tissues. Although, plasma transferrin compartment is considered relatively small, its iron content turns over every few hours, allowing iron concentrations to respond rapidly to changes in hepcidin concentrations.<sup>12-15</sup>

The role of hepcidin is mainly to regulate the absorption of dietary haeme, which is the main form of absorbable iron in human. Usually haeme is metabolized to ferrous iron by the enterocytes, however, its transfer to plasma will require ferroportin and hence is subjected to hepcidin-regulation.<sup>12-15</sup>

## 2.5 Treatment of iron deficiency anaemia

Although oral iron therapy is the most widely practiced treatment for iron deficiency anaemia, there are many issues that limit oral iron success in the management of IDA.

For instance, many patients do not respond adequately to oral iron therapy due to difficulties associated with ingestion of the tablets and their side effects, which can play a significant role in rates of compliance.<sup>16-17</sup>

The side effects of oral iron therapy include gastrointestinal disturbances characterized by colicky pain, nausea, vomiting, diarrhoea and or constipation, and occur in about 50% of patients taking iron preparations.<sup>6</sup>

Furthermore, the most widely prescribed oral iron is mainly composed of ferrous salts.<sup>18,19</sup> Ferrous salt is characterized by low and variable absorption rates and also its absorption can



be limited in conjunction with ingestion of certain foods as well as mucosal luminal damage.<sup>18-21</sup> Therefore, ferric compounds were introduced to avoid such obstacles. However, these compounds are generally less soluble and have poor bioavailability.<sup>21</sup>

The usual recommended oral iron sulphate dose for the treatment of iron deficiency should be at least 80 mg daily of elemental iron, which is equivalent to 250 mg of oral iron sulphate tablets (Abbott, Australasia Pty Ltd).

In addition to oral iron side effects, patients with chronic bowel disease do not absorb oral iron readily and thereby minimise the benefit received from oral iron treatment.<sup>21</sup>

Although it is debatable whether intravenous iron should be administered or would oral iron have the same effect, many queries remain and are required to be addressed in further research and randomised trials.

The major challenges in the management of IDA are related to the tolerability and side effects of iron therapy in its different forms. Therefore, it is crucial to determine the most appropriate form and dose of iron as well as duration of treatment in order to successfully replenish the iron stores. Traditionally, the oral iron was widely used worldwide, however the effectiveness of oral formulations, due to the several facts mentioned before, is compromised by lack of absorption, poor compliance, adverse effects (up to 56%) and discontinuation of treatment (up to 20%).<sup>6,18,21</sup>

On the other hand, parenteral iron seems to be an attractive alternative to oral iron and is likely to be more popular option due to the introduction of new intravenous iron preparations, which allow high doses of iron to be administered rapidly in a single treatment.

In the past, intravenous iron had been associated with undesirable and sometimes serious side-effects and was therefore limited in use.<sup>22-23</sup> However, in recent years, the new type II and III iron complexes have been developed which are better tolerated and can be used for rapid repletion of iron stores.<sup>24,25</sup> Despite increasing evidence of the safety of the newer preparations, both in pregnant and general populations, intravenous iron continues to be underutilised because of previous concerns with tolerability of older intravenous iron preparations.<sup>26</sup>

Review of infusions of iron dextran among 481 patients revealed that about 25% of patients had mild side effects that have been self-limited. However about 2% experienced severe allergic reactions and about 0.6% were considered as anaphylactic reactions. Most of these reactions occurred immediately during the infusion of the test dose.<sup>27</sup>

On the other hand, iron gluconate is considered to have a lower reaction rate and therefore a test dose is not recommended. During the 1990s, only 3.3 allergic events per million doses per year with iron gluconate were reported.<sup>28</sup> During mid 1970s to mid 1990s There were no life-threatening reactions recorded as a result of iron gluconate infusion.

In contrast, during the same period, there were 31 fatalities among 196 allergic/anaphylactic reactions were reported for iron dextran, with about 16% of case fatality rate.<sup>28</sup>

The high incidence of adverse reactions of iron dextran including serious adverse events have limited its application in practice.<sup>29-31</sup> Nonetheless, the application of iron gluconate is considered safe, it remains impractical in theory as it requires multiple infusions with huge implications on the often-limited health system resources as well as on patients' compliance. There are new forms of intravenous iron that have recently been developed and are available in some countries that permit treating physicians to administer safely relatively high doses of iron in a single dose treatment. Furthermore, relatively older and established iron preparation such as intravenous iron polymaltose (Ferrosig, Sigma Pharmaceuticals,

Australia) demonstrated a high safety profile in treatment of IDA in both obstetric and general populations without a maximum dose-limit for treatment of IDA.<sup>26</sup> The total dose of IV iron polymaltose is calculated according to the patient's body weight and entry Hb level according to the product guidelines as following; iron dose in mg (50 mg per 1 ml) = body weight (maximum 90 kg) in kg x (target Hb (120 g/L) - actual Hb in g/L) x constant factor (0.24) + iron depot (500).<sup>26</sup> Recent reports demonstrate the feasibility of rapid infusion over 2 hours.<sup>26,32,33</sup> However, a test-dose of iron polymaltose (100 mg) should be first administered over 30 minutes and premedication is recommended prior to iron treatment for better toleration (antihistamine and or low dose steroids).<sup>26,32,33</sup>

Furthermore, in 2009, the United States Food and Drug Administration (FDA) approved ferumoxytol (AMAG Pharmaceuticals, Inc., USA)<sup>34</sup> for the treatment of iron-deficiency anaemia in adult patients with chronic kidney disease (CKD).<sup>34</sup> However, the maximum dose allow only 510 mg of ferumoxytol in a single administration and is limited to use initially in CKD, although with the expected expansion of its spectrum to include other forms of IDA.<sup>35</sup> Another form of iron is ferric carboxymaltose (Vifor Pharma, Glattbrugg, Switzerland), which can be rapidly administered in 15 minutes in doses of 15 mg/kg body weight, with a maximum dose of 1000 mg.<sup>36,37</sup> There is no need for a test-dose of ferric carboxymaltose and its use is not restricted as ferumoxytol. More recently, in July 2010 a new intravenous iron isomaltoside (*MonoFer*, Pharmacosmos A/S, Holbaek, Denmark)<sup>38</sup> is introduced without the requirement of a test dose and it can be administered in 60 minutes at a rate of 20 mg/kg body weight in a single infusion without a maximum dose.<sup>38,39</sup> Iron isomaltoside administration was effective, safe, and was well tolerated when used to replenish iron stores in patients with anaemia of CKD.<sup>39</sup>

Intravenous iron including iron sucrose was employed in randomised controlled trials with improved effectiveness of intravenous iron only or in combination with oral iron compared to oral iron only based on Hb levels.<sup>40,41</sup>

A single IV iron sucrose dose has been reported to produce an increased incidence of thrombosis (9/41; 22%).<sup>42</sup> In contrast, 6 small doses of intravenous iron sucrose were administered over a three-week period without infusion-associated thrombosis as intravenous iron sucrose was administered in 5 daily doses to 45 pregnant women, also well tolerated.<sup>34</sup> In the first study, utilising intravenous iron sucrose, there was no significant difference between intravenous iron sucrose versus oral iron sulphate in the Hb levels at any time as measured at days 8, 15, 21, 30 and at delivery,<sup>42</sup> while in the second trial, with the 6 small doses of iron sucrose, there was a significant difference in Hb levels in favour of the intravenous iron sucrose group as measured at 2 and 4 weeks after administration of IV iron and at delivery.<sup>40</sup>

However, both trials administered IV iron sucrose at the expense of a vastly greater effort from the patients as well as extra demands on hospital resources.<sup>40,41</sup>

Certainly, the new intravenous iron preparations represent a medical revolution in effective, rapid and safe iron repletion in the management of iron deficiency anaemia.<sup>34-39</sup> This will reflect positively in the treatment of IDA in different populations by application of a single high-dose intravenous iron treatment with subsequent repletion of the iron stores effectively and hence, to improve subjective and objective outcomes in IDA.

Although iron deficiency is a precursor of IDA, many clinical studies treat it similarly to IDA. In case of severe IDA, a blood transfusion has been the traditional efficient approach to correct the anaemia, especially if patients did not respond to oral iron therapy or when a rapid correction of anaemia is clinically required.

Currently, the development of new intravenous iron formulations that offer higher doses in a single administration has provided the treating physicians with the opportunity to employ intravenous iron as an effective, rapid and safe treatment for IDA<sup>34-39</sup> avoiding the use of blood transfusion with its known hazards.<sup>43</sup> There are increasing evidence-based research that support the safety and efficacy of IV iron in IDA. There is also increasing evidence for inadequacy of oral iron in terms of adverse effects, lack of compliance as well as lack of absorption and slow and often questionable effect in IDA patients, especially in patients with ongoing blood loss.<sup>44-47</sup>

A common requirement across the range of clinical situations is the need for safe, effective higher, less frequent doses to achieve optimal clinical outcomes. The major goals of such strategy include overall cost reduction, relief to overstretched health system(s), improved patient convenience, improved compliance, preservation of venous access and reduced blood transfusion.<sup>35-41,43,46</sup> This will ultimately reduce the demand for blood transfusions, especially in the case of short supply. Furthermore, some of the new iron preparations such as ferric carboxymaltose and iron isomaltoside, do not require a test dose and therefore, ease the application of intravenous iron in a timely and cost effective fashion. This certainly will enhance the use of intravenous iron in clinical practice.

The WHO identified the problem of IDA as the most debilitating nutritional deficiency worldwide in the twenty first century. Such problem, if left untreated and not addressed properly can have a devastating effect on entire populations with adverse socio-economical consequences. Therefore, the use of intravenous iron should be considered as an effective, rapid and safe treatment option in some clinical scenarios with intravenous iron being employed to avoid or reduce the demand for blood transfusions or when rapid repletion of iron stores are required. Treatment options for IDA should consider the recently developed intravenous iron formulations, which is considered a milestone in the management of IDA.

Overall, the developing world is most vulnerable, especially the poorest and the least educated countries that are disproportionately affected by iron deficiency, and therefore they will gain the most by eradication of IDA. Therefore, awareness of the magnitude and scale of the IDA problem will help in recognising the most appropriate ways of diagnosis and treatment, which is crucial to overcome such devastating health problem. Perhaps consensus guidelines set by world experts in managing IDA incorporating new intravenous iron therapies are warranted.

### 3. Vitamin B12 deficiency anaemia

Cobalamin (vitamin B12) along with folic acid is normally required for DNA synthesis. Deficiency of one or both can cause defect in DNA synthesis, with lesser defect in RNA and protein synthesis, leading to a state of unbalanced cell growth and impaired cell division. The aberrant DNA synthesis causes arrest in S phase of cell cycle, affecting mitosis and cell division. This results in nucleocytoplasmic asynchrony and megaloblastic anaemia.<sup>1</sup>

#### 3.1 Cobalamin

Cobalamin is a complex organo-metallic compound in which the cobalt atom is situated within a corrin ring. The two active coenzyme forms are methylcobalamin and 5-deoxyadenosyl cobalamin<sup>1</sup>.



### 3.2 Main functions of cobalamin<sup>2</sup>

1. Conversion of methyl malonyl coA to succinyl coA in the mitochondria.
2. Methylation of homocysteine to methionine in the cytoplasm.

### 3.3 Effects of cobalamin deficiency

- a. Impairment of DNA synthesis  
Cobalamin deficiency causes reduced methionine, which leads to reduced tetrahydrofolate and high methyl tetrahydrofolate in the cells (methyl folate trap hypothesis). This in turn causes low dTMP synthesis with high dUMP levels which results in impairment of DNA synthesis due to uridine for thymidine substitution in base pairing.
- b. Defective myelin synthesis and neurological problems.  
Cobalamin and folate have fundamental roles in CNS function at all ages, especially the methionine-synthase mediated conversion of homocysteine to methionine, which is essential for nucleotide synthesis and genomic and non-genomic methylation<sup>3</sup>. Prolonged cobalamin deficiency causes defective conversion of propionate to succinyl coA and also causes high serum methyl malonic acid and homocysteine. Both of these can cause defective myelin synthesis and neurological dysfunction, since methionine is required for synthesis of choline.
- c. Venous and arterial thrombosis.  
Plasma homocysteine levels are increased in both folate and cobalamine, which can lead to venous and arterial thrombosis<sup>4</sup>.

### 3.4 Sources of cobalamin and dietary requirements

Cobalamin cannot be synthesized in human beings and needs to be supplied in the diet. Animal sources like meat, liver, fish, egg, milk and cheese are good sources of cobalamin. The estimated daily requirement of cobalamin is 1 mcg/day. The recommended daily allowance is 2.4 mcg/day. The daily requirement is so small relative to stores that deficiency typically takes years to develop in adults.<sup>5</sup>

### 3.5 Absorption, transport and cellular uptake

Absorption:

1. Stomach  
Gastric digestion releases cobalamin from the bound proteins. Gastric R-binder (also called haptocorrin) binds with cobalamin forming cobalamin - R binder complex. R-binder is also present in saliva, milk, gastric juice, bile, plasma and phagocytes.
2. Duodenum:  
Cobalamin - R binder complex is digested by pancreatic proteases. Cobalamin binds to Intrinsic Factor (IF). IF is produced by gastric parietal cells and is resistant to proteolytic digestion. IF has two binding sites, one for cobalamin and another for cubulin in Ileal cells.
3. Distal ileum:  
In the Ileal mucosal cell, IF is bound to cubulin. IF is destroyed and cobalamin binds to TCII forming a complex and absorbed into the blood.
4. Blood:  
Cobalamin - TCII complex in the blood is rapidly taken up by liver, bone marrow and other cells. Most cobalamin in the blood is bound to TCI, present in secondary granules of neutrophils, a group closely related to R binder. The function of TCI is not known.

5. Cellular uptake:  
Cobalamin – TCII complex is rapidly taken up by liver, bone marrow and other cells. Cobalamin – TCII is released into lysosomes. Lysosomal degradation leads to cobalamin release. Most of the cobalamin (~95%) is bound to two intracellular enzymes.
  - a. Methyl malonyl coA mutase in the mitochondria catalyses methyl malonyl coA to succinyl coA.
  - b. Methionine synthase in the cytosol: Methyl cobalamin acts as coenzyme for methionine synthase allowing transfer of methyl group from homocysteine to methionine. 5 methyl tetrahydrofolate donates methyl group to cobalamin thus regenerating methyl cobalamin.

### 3.6 Causes of cobalamin deficiency

- a. Nutritional cobalamin deficiency:

Causes: Strict vegans,<sup>6</sup> breast-fed infants of mothers with low cobalamin levels.

- b. Cobalamin malabsorption

1. Intrinsic Factor deficiency

Pernicious anaemia

Total gastrectomy

2. Food-bound cobalamin malabsorption (FBCM)

Gastritis can cause FBCM. Progression of anaemia is slower than in IF-related malabsorption and may extend beyond a decade.<sup>7</sup>

3. Disorders causing cobalamin malabsorption in small intestine:

- Pancreatic insufficiency
- Blind loop syndrome
- Fish tape worm (*Diphyllobothrium latum*)
- Mucosal damage :

Causes: Tropical sprue, nontropical sprue, Crohn's disease , Small intestinal tumours like lymphoma, granulomatous disease.

4. Other causes of cobalamin deficiency

Gastric achlorhydria

Partial gastrectomy

- Drugs: H2 receptor antagonists, proton pump inhibitors, Cholestyramine, Neomycin etc.

### 3.7 Pernicious Anaemia (PA)

PA is the most common cause of cobalamin deficiency is intrinsic factor deficiency due to atrophic gastritis or autoimmune destruction of parietal cells. The age of onset is usually after 40 years and more common in Northern European descent.

In autoimmune PA, the gastric parietal cells are affected by cytotoxic T cells. There is an increased incidence of circulating antibodies – antiparietal cell antibodies (90%) & anti-intrinsic factor antibodies (60%). PA can be associated with other autoimmune disorders like Grave's disease, Hashimoto's thyroiditis, Addison's disease and hypoparathyroidism.

Gastric atrophy affects acid and pepsin areas of the stomach while the antrum is spared. Atrophic gastritis usually precedes the onset of megaloblastic anaemia by many years. All

the cells which have a high proliferation exhibit megaloblastic changes, e.g. epithelial cells lining the gastrointestinal tract (buccal mucosa, tongue and small intestine), cervix, vagina, and uterus. There is a higher risk of gastric cancer and carcinoids in patients with pernicious anaemia.<sup>8</sup>

### 3.8 Clinical features of cobalamin deficiency

Haematologic: Pancytopenia with megaloblastic anaemia

Cardiopulmonary: Congestive heart failure

Gastro-intestinal: Beefy red tongue (glossitis), broad spectrum malabsorption, diarrhoea

Skin: Melanin pigmentation, premature greying of hair

Genitals: Cervical and uterine dysplasia

Reproductive: Infertility or sterility

### 3.9 Central nervous system (CNS)

CNS involvement is unique to cobalamin deficiency. Peripheral nerves, posterolateral columns of spinal cord, cerebrum, optic nerve and rarely autonomous nervous system are affected. Pathological changes are demyelination, axonal degeneration and neuronal death. Symptoms are paraesthesia, numbness in extremities, weakness and ataxia. Psychotic changes can occur in cobalamin deficiency, which can vary from mild irritability and forgetfulness to severe dementia or frank psychosis.

### 3.10 Lab investigation in megaloblastic anaemia

#### 3.10.1 Full blood count & blood film

High MCV usually precedes anaemia. Low red cell count, Hb and reticulocyte counts are common. Low white cell count and low platelet counts can occur in moderate to severe deficiency.

Blood film shows macro-ovalocytes, hypersegmented neutrophils (greater than 5% PMNs with more than five lobes or a single PMN with more than six lobes are pathognomonic). In severe deficiency, leuko-erythroblastic blood picture, tear drop poikilocytes, basophilic stippling, Howell Jolly bodies, nucleated red cells and Cabot's ring can be seen.

#### 3.10.2 Bone marrow analysis

Hypercellularity is prominent in all the three cell lines. Erythroid hyperplasia is more marked than the others. Abnormal erythropoiesis with abnormally large red cell precursors (megaloblasts) with less mature nuclei (nuclear - cytoplasmic asynchrony) is common. Nuclear chromatin is more dispersed with fenestrated pattern, a characteristic feature of megaloblastic anaemia.

In severe megaloblastic anaemia up to 90% of RBC precursors are destroyed before they become mature, when compared to 10 % in normal marrow (ineffective erythropoiesis).

Abnormal leucopoiesis - giant metamyelocytes and band forms are characteristic. Hypersegmented neutrophils are also seen in bone marrow. Abnormal megakaryocytes can be seen (pseudohyperdiploidy).

#### 3.10.3 Serum cobalamin levels<sup>9</sup>

Normal levels : 120 - 680 pmol/L measured using Immunoassay.

The limitations of serum cobalamin levels are

Falsely low levels (in patients with normal cobalamin)  
Severe folate deficiency (in 30% of patients)  
Low TC- I levels  
Physiologically low levels in pregnancy  
Intake of large doses of Vitamin C  
Falsely normal or high levels (in patients with low cobalamin)  
Myeloproliferative disorders (Cobalamin binders like TC-I &TC-II are increased)  
Acute liver disease (release of cobalamin from hepatocytes).

3.10.4 Other tests

3.10.4.1 Schilling test

The Schilling test measures cobalamin absorption by assessing increased urine radioactivity after an oral dose of radioactive cobalamin. Malabsorption due to any cause produces low radioactivity in urine. The test is useful in demonstrating that the anaemia is caused by an absence of IF. Schilling test helps to identify abnormal IF-related absorption and also to distinguish between gastric and intestinal defects.  
If the Schilling test result is normal, non-malabsorptive disorders and FBCM are considered. A modified absorption test, in which the test dose of cobalamin is bound to food, was created specifically to identify FBCM.<sup>10</sup>

3.10.4.2 Serum homocysteine and methyl malonic acid

Elevated serum methylmalonic acid and homocysteine levels are found in patients with cobalamin deficiency. Clinical deficiency often features serum MMA above 1000 nmol/L and homocysteine above 25 uM. In folate deficiency, serum methylmalonic acid levels are normal and homocysteine levels are high.<sup>11, 12,13</sup>

Patient Condition	Homocysteine	Methylmalonic Acid
Healthy	Normal	Normal
Vitamin B-12 deficiency	Increased	Increased
Folate deficiency	Increased	Normal

Table 1. Serum homocysteine and methylmalonic acid values in healthy persons, cobalamin and folic acid deficiency

The advantage of these tests is they measure tissue vitamin stores and may diagnose the deficiency even when the serum cobalamin and folate levels are borderline or normal.

3.10.4.3 Other tests

1. The indirect bilirubin level may be elevated because pernicious anaemia causes haemolysis associated with increased turnover of bilirubin. The serum lactic dehydrogenase (LDH) concentration usually is markedly increased.
2. Intrinsic Factor (IF) antibodies in serum by Immunoassay.<sup>14</sup>
3. Type 1 (blocking) antibody prevents the attachment of vitamin B12 to intrinsic factor: present in 50-60% of patients with pernicious anaemia. Type 2 (precipitating) antibody

prevents attachment of the vitamin B12-intrinsic factor complex to ileal receptors: present in 30% of patients with pernicious anaemia, and only in those who also have Type 1 antibodies. IF antibody has high specificity for PA (>95%). It is used to help diagnose when pernicious anaemia is suspected. As recent vitamin B12 administration is associated with a high rate of false positive results the sample must be collected prior to commencing therapy or at least one week after vitamin B12 administration. This test shows rarely false positivity in diabetes and thyroid disorders.

#### 4. Parietal cell antibodies

Parietal cell antibodies can be measured using indirect IF. Antibodies react with sub-units of the gastric parietal cell proton pump. Antibodies are positive in 80% of patients with pernicious anaemia and in 40-50% of patients with other organ specific autoimmune diseases.<sup>15</sup>

## 4. Treatment

### 4.1 Cobalamin deficiency

#### 4.1.1 Specific replacement therapy

The 1000-mcg intramuscular dose begins repletion of stores (up to 150 mcg is retained from that injection by most patients).<sup>5</sup> Cyanocobalamin and hydroxocobalamin are commonly available preparations. 8 to 10 injections are given over the first 2 to 3 months followed by monthly injections.<sup>16</sup> Hydroxocobalamin injections can be spaced at twice the interval for cyanocobalamin.<sup>17</sup> The toxicity of cobalamin is minimal with rare allergic reactions which can be anaphylactic.<sup>18</sup>

In a randomized study with cobalamin deficiency, 2 mg of cyanocobalamin administered orally on a daily basis was as effective as 1 mg administered intramuscularly on a monthly basis.<sup>19</sup> For patients who refuse monthly parenteral therapy or prefer daily oral therapy or in those with disorders of haemostasis, cobalamin (1–2 mg/day as tablets) can be recommended for patients with cobalamin malabsorption (where cobalamin is passively absorbed at high doses).<sup>1</sup>

Patients with FBCM may need to take cobalamin supplements on an empty stomach to prevent in vitro binding of cobalamin to food. 1000 mcg oral doses may be necessary in many cases of FBCM, but the undesirable effects of long term high doses, if any, are not known.<sup>20</sup>

#### 4.1.2 Response to treatment

The response to treatment is generally predictable and can be used as a therapeutic trial. Patients have a sense of well-being within 12 to 24 hours, which is an early feature of response. In bone marrow the megaloblastic erythropoiesis starts changing to normoblastic within 12 hours and complete resolution by 48 hours. Brisk reticulocytosis starts at 3 to 4 days and peaks at 5 to 7 days. Hypersegmented neutrophils continue to remain in the blood for 10 to 14 days. Mean corpuscular volume (MCV) will take eight weeks or more to normalize.<sup>1</sup> All these responses will be impaired if there is associated iron deficiency, anaemia of chronic disease or hypothyroidism.

Neurologic improvement also begins within the first week and is typically complete in 6 weeks to 3 months. Its course is not as predictable as a haematologic response. Severe hypokalemia can occur after cobalamin therapy, which requires careful monitoring and management.



#### 4.1.3 Causes of non-responsiveness of megaloblastosis to medication

1. Wrong diagnosis (eg: Myelodysplastic syndrome)
2. Combined cobalamin + Folate deficiency ,medication with one vitamin
3. Drugs eg: Hydroxyurea, azathioprine
4. Factors associated with B12 deficiency causing impaired response
  - c. Iron deficiency
  - d. Haemoglobinopathy
  - e. Hypothyroidism

#### 4.2 Transfusions

Complications can occur during transfusions, particularly congestive heart failure in elderly. Transfusion should be restricted to symptomatic anaemia, rather than by low haemoglobin values. In severe anaemia, exchange transfusion after removing 250- 300ml of anaemic blood and replacing packed red cells may be beneficial.

#### 4.3 Maintenance regimens

High dose cobalamin tablets (1000 mcg) can be used for maintenance therapy. Despite the advantages of ease, cost, and comfort, oral therapy has its own limitations. Oral cobalamin is less effectively absorbed after a meal than when fasted.<sup>21</sup> Monthly parenteral cobalamin injections are a better alternative in patients who are non-compliant with oral therapy.

#### 4.4 Cobalamin prophylaxis in clinical practice

The value of general supplementation or dietary fortification with cobalamin are not proven.<sup>22</sup> In some situations, like strict vegetarians, patients with gastric surgery and in elderly persons, life-long supplementation with cobalamin will be essential.

### 5. Folate deficiency anaemia

Folic acid is also known as pteroyl-monoglutamic acid. Fruits and vegetables constitute the main dietary source of the vitamin. Dietary folic acid is heat labile and may be destroyed by cooking. The daily requirement is usually about 50 mcg. The requirement may be increased to many folds during pregnancy.

Folates in various foodstuffs are largely conjugated as polyglutamates. Conjugases in the lumen of the gut convert polyglutamates to mono- and diglutamates, which are readily absorbed in the proximal jejunum. Plasma folate is primarily in the form of N5-methyltetrahydrofolate which is a monoglutamate and is transported into cells by a carrier. In the cell, the N5-methyl group is removed and the folate is then converted again to the polyglutamate form. Conjugation to polyglutamate may be useful for retention of folate within the cell.

The normal body store of folic acid is 5 to 20 mg. Nearly 50% of the body stores are present in the liver. Folate deficiency usually occurs within 4 to 5 months with dietary deficiency, in contrast to cobalamin deficiency which takes many years.

#### 5.1 Role of folate in DNA synthesis

Folate serves as an intermediate carrier of 1 carbon fragment and is essential for denovo synthesis of purines, dTMP and methionine. Its active form is tetrahydrofolate, which acquires 1 carbon from serine and converted to glycine.

For purine synthesis, the 1 carbon is oxidised to formic acid, then transferred to substrate. For methionine synthesis, cobalamin is required and 1 carbon fragment is reduced to the level of methyl group, which is then transferred to homocysteine. In these reactions, the cofactor is released as tetrahydrofolate which can immediately participate in another 1-carbon transfer cycle.

Conversion of dUMP to dTMP is catalysed by thymidylate synthase and dihydrofolate is released. To participate in further 1- carbon transfer cycle, the dihydrofolate is catalysed by dihydrofolate reductase to tetrahydrofolate.

## 5.2 Folate deficiency

### 5.2.1 Causes

1. Inadequate intake  
Alcoholics, infants, anorexia nervosa, malnutrition, prolonged cooking of vegetables.
2. Increased requirements
  - a. Pregnancy and lactation
  - b. Infancy and childhood
  - c. Haemolytic anaemias
  - d. Cancers
  - e. Exfoliative dermatitis
3. Malabsorption
  - a. Tropical sprue and non-tropical sprue
  - b. Partial gastrectomy
  - c. Crohn's disease
  - d. Intestinal Lymphoma
4. Impaired Metabolism
  - a. Alcoholism
  - b. Dihydrofolate reductase inhibitors: Methotrexate, pentamidine, trimethoprim
5. Reduced hepatic stores
  - a. Alcoholism
  - b. Chronic liver disease and cirrhosis
  - c. Hepatic malignancy

## 5.3 Alcoholism

The common cause of Folate deficiency is alcohol intake. Folate deficiency in alcoholics can be attributed to multiple factors.

- a. Dietary malabsorption
- b. Reduced food intake
- c. Depletion of liver stores of folate
- d. Impaired intracellular folate utilization

Prolonged and excessive alcohol can lead to megaloblastic changes in the bone marrow.

## 5.4 Tropical sprue / coeliac disease

In tropical sprue and coeliac disease, low folate levels are caused by folate malabsorption. Steatorrhoea is the major symptom.

In tropical sprue there will be high foecal fat and jejunal biopsy shows subtotal or total villous atrophy. In coeliac disease, d- xylose test is positive.

In coeliac disease, a gluten free diet can correct folate malabsorption.

### 5.5 Anti convulsant drugs

Drugs like phenytoin and phenobarbitone can cause folate deficiency. This is usually due to inhibition of dietary folate absorption caused by reduced levels of small intestinal conjugases.

### 5.6 Pregnancy

Since the foetus accumulates folate, the demand is high during pregnancy.

### 5.7 Haemolytic states

Haemolytic states like hereditary spherocytosis, auto-immune haemolytic anaemia, sickle cell anaemia, thalassaemias and paroxysmal nocturnal haemoglobinuria cause erythroid hyperplasia. Increased erythroid turnover causes an increase in folate demand, thus causing folate deficiency.

### 5.8 Exfoliative disorders

Patients can lose folate in exfoliated skin. In exfoliative skin disorders, folate deficiency can occur.

### 5.9 Neoplastic disorders

In acute leukaemias, myeloproliferative disorders, myeloma and metastatic carcinomas, the neoplastic tissue utilize folate more rapidly than the host tissue.

### 5.10 Clinical features of folate deficiency

Clinical features of folate deficiency are similar to cobalamin deficiency, except that neurological manifestations are not common in folate deficiency.

Haematological – pancytopenia with megaloblastic anaemia

Cardiopulmonary - congestive heart failure

Gastrointestinal – glossitis, broad spectrum malabsorption and diarrhoea

Folate deficiency can also be implicated in:

1. Increased arteriosclerosis risks due to elevated homocysteine<sup>1</sup>
2. Foetal neural tube defects<sup>2</sup>
3. Cancer pathogenesis<sup>3</sup>

### 5.11 Laboratory investigations

#### 5.11.1 Full blood count & blood film

The features are similar to cobalamin deficiency. Macrocytic anaemia with ovalocytes and tear drop cells are seen in the blood film. Hypersegmented neutrophils are commonly seen. Neutropenia and thrombocytopenia are less common. In rare cases, the absolute neutrophil count can drop below  $1.0 \times 10^9/L$  and the platelet count below  $50 \times 10^9/L$ .

#### 5.11.2 Bone marrow analysis

Bone marrow features are also similar to that seen in cobalamin deficiency. Hypercellularity is prominent in all the three cell lines. Erythroid hyperplasia is more marked than the others.

Abnormal erythropoiesis with abnormally large red cell precursors (megaloblasts) with less mature nuclei (nuclear – cytoplasmic asynchrony) is common.

### 5.11.3 Serum folate levels

Normal serum folate levels are 7-45 nmol/L measured by immunoassay.

Limitations of serum folate assay:

Levels vary with levels of folate in the recent diet. Falsely high values of serum folate can occur in haemolysis (in vivo and in vitro) and in cobalamin deficiency.

### 5.11.4 Red cell folate levels

Normal serum folate levels are 360-1400 nmol/L, measured by immunoassay. Red cell folate is a good index of folate stores and not affected by dietary folate intake. Low red cell folate levels are a better predictor for folate deficiency than low serum folate levels.

However, there are few limitations in this assay. Low to subnormal range occurs only after all the stores are depleted. In two-thirds of patients with severe cobalamin deficiency, falsely low red cell folate levels are common. Since reticulocytes have increased folate concentrations, haemolytic states may produce falsely normal or high red cell folate despite folate deficiency.

### 5.11.5 Serum homocysteine and methyl malonic acid

In folate deficiency, serum methyl malonic acid levels are normal and homocysteine levels are high.<sup>4</sup>

## 6. Treatment of folate deficiency

The usual treatment dose of folic acid tablets is 1mg/day. Sometimes up to 5mg/day may be required as in haemolytic anaemias. Adequate absorption with such doses usually occurs even in chronic folate malabsorption. Therapy should be continued until complete hematologic recovery. If the underlying cause is not correctable, folate should be continued. Folinic acid (leucovorin) can be used to rescue drugs with antifolate activity e.g. antimetabolites (methotrexate or 5-fluorouracil) or other drugs like sulfamethoxazole- trimethoprim and pentamidine. Haematological response after folate is similar to cobalamin deficiency.

### 6.1 Prophylaxis

Folic acid prophylaxis is essential in the following situations

- Pregnancy and lactation: The dose is usually 400mcg daily.
- Mothers at risk of delivery of neural tube defects: The dose of folic acid is 4mg/day during the peri-conception period and throughout the first trimester.
- Haemolytic anaemias and hyperproliferative haematological states: The dose is usually between 1mg to 5mg daily.
- Patients with rheumatoid arthritis or psoriasis on medication with methotrexate.<sup>6</sup>

## 7. Other rare nutritional deficiencies that can cause anaemia

Deficiencies of trace elements like copper and selenium can cause anaemia.

Copper is present in legumes, meats, and nuts with a very low daily requirement.<sup>1</sup> It is absorbed through the mucosa of the stomach and proximal duodenum.<sup>2</sup>

Copper is an essential trace metal acting as a ligand to many proteins and enzymes.<sup>2</sup> Dopamine  $\beta$ -hydroxylase is a copper containing enzyme responsible for conversion of dopamine to norepinephrine, which mediates many neurologic functions. Copper also acts as a ligand to ferroxidase II, which oxidizes iron, helping in the mobilization and transport from hepatic stores to the bone marrow for erythropoiesis.<sup>3</sup> Thus, copper deficiency results in excessive iron in the liver but defective transport of iron to the marrow for effective erythropoiesis.<sup>4</sup>

### 7.1 Causes of copper deficiency

Acquired copper deficiency is rare. The few potential causes are

1. Gastric and bariatric surgery causing malabsorption<sup>5,6</sup>
2. Intravenous hyperalimentation without copper supplementation
3. Hyperzincaemia
4. Menkes disease, an inherited copper deficiency disorder, in which there is a failure of transporting absorbed copper to the rest of the body from mucosal cells.

### 7.2 Haematological manifestations of copper deficiency

Copper deficiency can cause anaemia and leukopenia. Sideroblastic changes and nuclear maturation defects in erythroid precursors leading to anaemia have been observed in patients with copper deficiency.<sup>1</sup> Peripheral smear often reveals sideroblastic anaemia with hypochromic microcytic red cells. Leucopenia and thrombocytopenia are less common.<sup>7</sup> The MCV is normal or increased in anaemia of copper deficiency.

### 7.3 Other manifestations

Copper deficiency is known to cause neurologic deficits due to demyelination. Manifestations include myelopathy, polyneuropathy, ataxia and optic neuritis.<sup>8</sup> The combination of myelopathy, polyneuropathy and anaemia in copper deficiency can mimic the deficits seen with vitamin B12 deficiency.

### 7.4 Treatment

Copper deficiency can be treated with either oral copper supplementation or intravenous copper.<sup>9</sup> If zinc intoxication is present, discontinuation of zinc may be sufficient to restore copper levels back to normal, but this is usually a very slow process.<sup>9</sup> They will also need to take copper supplements in addition to stopping zinc consumption. Haematological manifestations are often quickly restored back to normal.<sup>9</sup> The neurological symptoms will often cease, but the symptoms are not always restored back to normal.

### 7.5 Selenium

Selenium is a vital trace element for efficient and effective operation of many functions of the human immune system.<sup>10,11</sup> Selenium is a mineral that is required by the body in trace amounts. Daily requirement of selenium is 50 micrograms. It is present in most organs of the body like kidneys, spleen, liver, pancreas. Selenium is a component of glutathione peroxidase and can be used as an antioxidant and also plays a large role in cell metabolism and cancer prevention.



### 7.5.1 Selenium deficiency

Selenium deficiency is relatively rare in healthy well-nourished individuals.

Causes of selenium deficiency

1. Eating foods predominantly grown in selenium-deficient soil.
2. Severely compromised intestinal function
3. Total parenteral nutrition
4. Gastrointestinal bypass surgery

Manifestations of a selenium deficiency include cardiovascular disease, nerve degeneration, hypothyroidism, arthritis and anaemia. A selenium deficiency may even increase the chances of developing some forms of cancer.

Selenium deficiency may play a role in causing or aggravating anaemia as glutathione peroxidase protects red blood cells from free radical damage and destruction. In a prevalence study there was low serum selenium found independently associated with anaemia among older men and women.<sup>12</sup> Mean serum selenium among non-anaemic and anaemic adults was 1.60 and 1.51  $\mu\text{mol/L}$  ( $P=0.0003$ ). The prevalence of anaemia among adults in the lowest to highest quartiles of serum selenium was 18.3, 9.5, 9.7 and 6.9%, respectively ( $P=0.0005$ ).<sup>12</sup>

### 7.5.2 Supplements

There are many forms of selenium supplements including organic selenium rich yeast, selenium in the form of selenomethionine, and inorganic sodium selenite. Selenium yeast increases the blood selenium levels and sodium selenite helps to increase the activity of glutathione peroxidase. Organic selenium is better absorbed and less toxic than the inorganic forms. People who are at risk of selenium deficiency will benefit from supplements.

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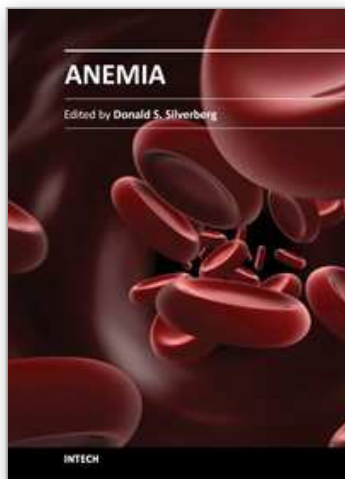
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This book provides an up- to- date summary of many advances in our understanding of anemia, including its causes and pathogenesis, methods of diagnosis, and the morbidity and mortality associated with it. Special attention is paid to the anemia of chronic disease. Nutritional causes of anemia, especially in developing countries, are discussed. Also presented are anemias related to pregnancy, the fetus and the newborn infant. Two common infections that cause anemia in developing countries, malaria and trypanosomiasis are discussed. The genetic diseases sickle cell disease and thalassemia are reviewed as are Paroxysmal Nocturnal Hemoglobinuria, Fanconi anemia and some anemias caused by toxins. Thus this book provides a wide coverage of anemia which should be useful to those involved in many fields of anemia from basic researchers to epidemiologists to clinical practitioners.

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